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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/826,157	LINDQUIST ET AL.	
	Examiner	Art Unit	
	MARIA B. MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/26/07 and 4/21/08*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,3,4,7-17,22,23 and 27* is/are pending in the application.

4a) Of the above claim(s) *23 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,7-17 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/13/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 4/21/08 and arguments filed 9/26/07. Claims 1, 3, 4, 7-17, 22, 23 and 27 are pending in the application. Claims 23 and 27 are withdrawn and therefore, claims 1, 3, 4, 7-17 and 22 are under examination.

Claims 23 and 27 are commensurate in scope with the allowed products. However, until an elected product claim is found allowable, an otherwise proper restriction between product claims and process claims may be maintained. At such a time that an allowable claim is identified, claims 23 and 27 will be examined to ensure that they also meet all criteria for patentability including the requirements of 35 USC 101, 101, 103 and 112.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 119(e) as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application Nos. 60/463284 and 60/472317 filed respectively 4/16/03 and 5/20/03, fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. 112 for one or more claims of this application. Specifically, claim 16 is drawn to a yeast cell comprising a disruption in the PDR5 gene. However, utilization of a yeast cell comprising a disruption in PDR5 is not disclosed in the priority documents 60/463284 and 60/472317. Therefore, a priority date of 4/16/04 will be attributed to this limitation and instant claim 16.

Response to Argument

Applicants' arguments filed 9/26/07 have been fully considered but they are not persuasive. Applicants argue that the amendments amd remarks obviates a need to assess claim 16 in terms of the priority date. However, the rejection of claim 16 has been maintained for reasons below.

Claim Objections

Claim 1, 3, 4, and 13 are objected to because of the following informalities: The claim recommendation made in the office action mailed 3/26/07 has been reconsidered and slightly amended here. Recitation in claims 1 as well as 3 and 4, "wherein induction of production of the protein is toxic to the yeast cell" and "induction of expression" should be amended to --wherein the protein is toxic to the yeast cell-- and --wherein expression of the nucleic acid--. The amendment is recommended as recitation that induction of the expression is responsible for toxicity and cell growth arrest and loss of viability is not accurate as induction is limited to the

moment expression commences and does not in itself have much effect on the cell state. However, according to the specification it is the protein or the expressed product of the nucleic acid that affects the cell.

As well, in claim 1, the recitation "wherein the expression construct is integrated in the genome of the yeast cell" is redundant and inaccurate. The claim indicates in the preamble already that there are two expression constructs that are integrated constructs. It would be remedial to delete this phrase.

In claim 13, each of the fluorescent proteins require articles.

These are new objections. Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3, 4, 7-17 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a yeast cell comprising two integrated copies of an expression construct comprising a nucleic acid encoding a protein comprising wild-type alpha synuclein or mutant A53T under control of an inducible promoter wherein the protein is toxic to the cell such that the cell is non-viable, does not reasonably provide enablement for any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. **This is a new rejection.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

The specification teaches that alpha synuclein is associated with protein misfolding disease or condition such as neurological disorder or neurodegenerative conditions in humans. To this end, the specification teaches specifically that there are only two α-synuclein peptides, wild-type (WT) and mutant A53T (see e.g. page 44, line 5-8) that are toxic to yeast cells in ways that can be used to identify drugs which inhibit misfolding and/or abnormal processing of proteins and thus can be used in prevention or treatment . Specifically, the specification teaches that that yeast cells expressing these proteins "recapitulate hallmarks of abnormally processed protein biology such as 1) membrane association; 2) formation of inclusions; 3) differences in the behavior of wild type and A53T versus A30P; 4) ubiquitination; 5) toxicity; 6) interactions with mutant huntingtin (htt); 7) oxidative stress; and 8) inhibition of PLD". Hence, applicants proposed development of yeast cells comprising nucleic acid expressing toxic levels of alpha-synuclein for purposes of establishing cells exhibiting the toxic effects of alpha-synuclein (AS) to assay and analyze the toxicity of AS and methods of inhibiting these. Applicants have demonstrated in post-filing publications that two copies of a-synuclein are required to affect

growth and cell viability (see e.g. Cooper et al, 2006, page 324, col 2 and Outeira and Lindquist, 2003, page 1773).

The instant claims have been assessed and found to have a level of unpredictability for the following reasons. First, it is not clear how levels of protein are altered to attain the recited goals 1) wherein the protein is toxic to the cell 2) wherein expression of the nucleic acid renders the cells non-viable 3) wherein expression of the nucleic acid arrests growth of the cell and 4) wherein the cell expresses a toxicity inducing amount of the proteins. The specification simply teaches integration of two expression constructs wherein expression is under control of an inducible promoter and wherein expression results in loss of viability, Hence, it is not clear what distinguishes the ability of these peptides to mediate toxicity versus non-viability versus cell growth arrest. In fact, the only experimental procedures provided by applicants are use of cells wherein the expression vector is integrated into the yeast genome and A53T or WT synuclein is under control of an inducible promoter as demonstrated in figure 3 where expression results in cell death. Hence, the specification does not teach any how to manipulate levels of protein such that one could distinguish between toxicity, cell growth arrest or loss of viability. In fact, it appears that all inducible amounts are toxicity inducing amount of the proteins. The specification does not provide guidance as to how to express A53T or WT synuclein to cause non-viability versus growth arrest. Rather it appears that induction results in non-viability or toxicity in the cell and the event requires use of an inducible promoter.

As well, it is not clear how a toxicity inducing amount is achieved in the absence of an inducible promoter given the lethal affect of the protein on the cell. However, amendment to such a cell would result in a duplicate claim. As to construction of cells, the specification

teaches, "To express alpha synuclein proteins in yeast cells, a variety of expression constructs that permitted different levels of expression and different patterns of regulation of aS proteins were generated. For example, 2.mu. vectors are present in high copy and permit high levels of expression, but they have the disadvantage of varying in number from cell to cell and instability. Integrating constructs are extremely stable but produce lower levels of expression. Constitutive promoters allow expression in normal media, but inducible promoters allow to control the levels and timing of expression. Controllable expression is of particular interest when dealing with potentially toxic proteins, to enhance transformation efficiencies and avoid the accumulation of mutations in the genome that alter aS function and toxicity. Western blotting of aS, A53T, and A30P demonstrated similar levels of accumulation." Hence, it appears that the cells comprising integrated copies of expression vectors require the nucleic acid under control of an inducible promoter. Constitutive expression would not allow the cells to mature and grow. Given the lack of guidance in the specification, the large and diverse group of peptides recited and the highly unpredictable nature of the art, it is concluded that a person of skill in the art would have had to conduct undue experimentation in order to practice the claimed invention.

Claim Rejections - 35 USC § 102

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3, 4, 7-15, 17 and 22 are rejected under 35 U.S.C. 102(e) as being anticipated by Lindquist et al (US 7,045,290; see entire document) as evidenced by Sherman (Nine Yeast Vectors downloaded 7/18/08). **This rejection is maintained for reasons of record in the**

office action mailed 3/26/08 and restated below. The applied reference has common inventors with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Lindquist et al teach that expression of WT and mutant A53T is toxic to cells (see e.g. legend to figure 3). Lindquist teaches expression of WT and A52T in yeast cells via an integrative vector i.e. pRS304 and pRS306 for expression of alpha-synuclein (AS) as recited in claims 1, 9, 10, 17 and 18 as well as mutant and human AS as recited in claims 5, 6, 20 and 21 (see e.g. col 4, line 62- col 5, line 3). The AS may be a fusion peptide linked to a fluorescent peptide such as GFP as recited in claims 11-13. The yeast may be for example *Saccharomyces* as recited in claim 7 and 22 such as yeast cells comprising a mutation in pdr3 as recited in claims 14 and 15 (see e.g. col 10, line 28-49). As demonstrated in figure 3, the cells are non-viable (see growth characteristics in row 1 versus 2 for example. And as such, experience growth arrest as recited in claims 3 and 4. Vectors are described which allow integration of two copies or more as recited in claims 2 and 19 (see e.g. col 21) and as well comprise inducible promoters such as GPD (see e.g. col 23, line 38-60) as recited in claim 8.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lindquist et al (US 7,045,290; see entire document) as applied to claims 1-15 and 17-22 above, and further in view of Frate (US 2004/0115792; see entire document). **This rejection is maintained for reasons of record in the office action mailed 3/26/08 and restated below.**

Applicants claim a yeast cell comprising a disrupted PDR5 gene for expression of a toxic amount of a-synuclein.

The teachings of Lindquist et al are described above and are applied as before except; Lindquist et al do not teach use of a cell comprising a disruption in PDR5.

Frate teaches use of a yeast cell line comprising a disruption of PDR5 for testing genotoxicity and cytotoxicty of environmental contaminants. Frate chose use of this cell line as genes are responsible for export of toxic substances from the cell and their deletion means that toxic compounds can be analyzed in the context of the cell (see e.g. ¶ 0066-0067).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the cells comprising a deletion in pdr3 as taught by Lindquist et al with the cells comprising a pdr5 deletion as taught by Frate because Lindquist et al teach that it is within the skill of the art to assess toxicity of substances in a yeast cell expressing alpha-synuclein and because Frate teaches that it is within the ordinary skill of the art to use a pdr5 deficient cell as a host cell for analysis of toxic compounds. One would have been motivated to do so in order to receive the expected benefit of unhampered comparison of cell line as genes are responsible for export of toxic substances from the cell and their deletion means that toxic

compounds can be analyzed in the context of the cell. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Argument

Applicants' arguments filed 9/26/07 have been fully considered but they are not persuasive. Applicants argue that Lindquist does not disclose two copies of integrated alpha synuclein. In column 21, Lindquist provides for a variety of arrangements of alpha-synuclein in the cell. It is clear that more then one copy of nucleic acids capable of expressing aS are contemplated (see col 21 and table 5 which describes a variety of vectors that are preferred and provide any where from 1 to 2 to higher copy number plasmids). Hence, the specification contemplates more then one copy in a cell and specifically contemplates 2 copies in the cell. As well, the art teaches that Yip plasmids can be maintained in the cell in more then one copy per genome. However, of more pertinent disclosure is the teaching by Lindquist et al of use of pRS306 and pRS304 as integrative vectors for expression of aS and A53T. These are two specifically recited vectors in the instant claims. It can only be presumed that these vectors are recited as they specifically maintain the constructs at two copies per cell. These vectors since being used in Lindquist et al will inherently provide the same function in the prior art as in the instant invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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